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i. Title: Perioperative management of oral cleft repair: a retrospective chart review

ii. Running title: Perioperative management of oral cleft

iii. Authors:

Andrew James Shrimpton BChD MBChB<sup>1</sup>, Hannah Gill FRCA PhD <sup>1, 2, 3,</sup>

iv. Addresses:

1 - School of Physiology, Pharmacology & Neuroscience, University of Bristol,  
Biomedical Sciences Building, University Walk, Bristol BS8 1TD, United Kingdom

2 - Bristol Anaesthesia, Pain & Critical Care Sciences, Translational Health Sciences,  
Bristol Medical School, Level 7, Bristol Royal Infirmary, Bristol BS2 8HW, United  
Kingdom

3 - Department of Paediatric Anaesthesia, Bristol Royal Hospital for Children, Upper  
Maudlin St, Bristol BS2 8BJ, United Kingdom

Corresponding author contact details

Andrew Shrimpton

School of Physiology, Pharmacology and Neuroscience, University of Bristol,  
Biomedical Sciences Building, University Walk, Bristol BS8 1TD, United Kingdom

[andy.shrimpton@bristol.ac.uk](mailto:andy.shrimpton@bristol.ac.uk)

ORCID ID:0000-0001-6790-909X

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vi. Abstract and keywords

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## Background

Pre-clinical evidence has shown all common anesthetic drugs are toxic to the developing brain<sup>1</sup>. Despite numerous cohort studies and one randomised control trial (RCT)<sup>2</sup>, it remains unclear whether anesthetic-induced neurotoxicity exists and if intraoperative physiological disturbance plays a role. Well-designed RCTs with long-term follow-up are required to examine this. Infants requiring repair of oral cleft may provide an optimal clinical model; they often undergo multiple surgeries and have routine, nationally agreed, long-term speech and language assessments which extend into early adulthood. We aimed to describe anesthetic technique for repair of oral cleft in a pediatric tertiary referral hospital, and assess intraoperative physiological disturbance to inform design of a future RCT.

## Methods

We performed an anonymised retrospective case review of all infants undergoing repair of oral cleft during a 12month period; ethical approval was not required. Data were collected on anesthetic duration, perioperative drugs administered and intra-operative physiology. Age-adjusted MAC (minimum alveolar concentration) was calculated by dividing the end-tidal volatile concentration by the age-specific MAC<sup>3</sup>. Hypotension was defined using mean arterial pressure (MAP) into mild (MAP:36-45mmHg), moderate (MAP:26-35mmHg), and severe (MAP≤25mmHg)<sup>4</sup>. Normocarbida was defined as EtCO<sub>2</sub> between 4.0-6.0kPa.

## Results

38 infants underwent 53 surgeries to repair an oral cleft. Mean (SD) age: 6.9months (2.56), mean (SD) weight: 7.21kg (1.53). 15 infants had two surgeries, 28 surgeries (53.8%) were completed before 6months of age. 79% of infants had an isolated cleft with no other comorbidities.

Median (IQR) duration of anesthesia was 90mins (75-122.5); duration ranged from 45-180mins but only one case lasted under 60mins. Median (IQR) cumulative duration for the infants undergoing two surgeries was 225mins (175-240).

Volatile anesthetics were used for induction and maintenance of anesthesia in all cases. Mean (SD) age-adjusted MAC for isoflurane, sevoflurane and desflurane was: 0.70 (0.113), 0.88 (0.099) and 0.79 (0.066), respectively. Isoflurane was used in 73.5% of cases, sevoflurane in 20.7%. Five cases maintained with concomitant nitrous oxide had an isoflurane mean (SD) age-adjusted MAC of 0.51 (0.088); all these infants were under 6 months of age.

Mean (SD)  $\text{FiO}_2$  was 0.52 (0.134) with 46% of data points documented as  $\text{FiO}_2 \geq 0.5$ . Mean (SD)  $\text{EtCO}_2$  was within normal limits at 5.26kPa (0.736) but ranged from 3.2-8.0kPa. Hypocarbica was recorded 10 times in 10 cases (18.9%); hypercarbia was recorded 46 times in 21 cases (39.6%). Hypotension occurred in 23 (45%) cases: 20 mild, 3 moderate (see figure). All infants received intra-operative fluid, mean (SD) volume: 20.4ml/kg (6.64). No infants received vasopressors.

At induction: a muscle relaxant was used in 50 cases (atracurium 48, rocuronium 2), fentanyl in 50 cases, alfentanil in one. Surgical field infiltration of 0.25% bupivacaine occurred in 48 cases (90.6%). Intra-operative IV analgesia consisted of fentanyl (69.8%), morphine (15.1%) tramadol (15.1%), oxycodone (15.1%) and diclofenac (13.2%).

## Discussion

Infants undergoing oral cleft repair in our centre have high cumulative exposure to volatile anesthesia and commonly experience physiological homeostatic disturbances during these elective surgical procedures. Reducing or replacing these agents with drugs such as xenon or dexmedetomidine could potentially decrease the risk of anesthetic-induced neurotoxicity by the dual mechanism of decreasing exposure of the developing brain to neurotoxic agents, and reducing intraoperative physiological derangement<sup>5</sup>. Further reduction of anesthetic volatiles may be facilitated by the addition of opioids or intravenous lignocaine.

Regional blockade and sedation may be all that is required to provide optimal surgical conditions, the addition of volatile anesthetics may represent a relative overdose. Local anesthetic was used in most cases in our study and this may explain how a low mean age-adjusted MAC could be responsible for the intraoperative hypotension seen.

## Conclusions

Most babies born with cleft lip and/or palate undergo **corrective surgery** during infancy. They are commonly exposed to prolonged, repeated, anesthesia in the first year of life. Intraoperative physiological control is often deranged. With long-term neurological assessment part of their routine care, this elective surgical population may be an optimal model to investigate **anesthetic-induced neurotoxicity**.

## viii. References

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## ix. Tables

No table

## x. Figure legends

Figure: Scatterplot of MAP versus time for each volatile. Hypotension: (mild <45mmHg; moderate <35mmHg; severe <25mmHg)